FORM PTO-1390 **U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE**
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 9623 V/vmf/as

U.S. APPLN. NO. (If known, see 37 CFR 1.5): 10/009532

INTERNATIONAL APPLICATION NO.:	INTERNATIONAL FILING DATE:	PRIORITY DATE CLAIMED:
PCT/EP00/05356	09 JUNE 2000 (09.06.00)	14 JUNE 1999 (14.06.99)

TITLE OF INVENTION: CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITIONS

APPLICANT(S) FOR DO/EO/US: Roberto VILLA, Massimo PEDRANI, Mauro AJANI and Lorenzo FOSSATI

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [ ] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau. (see attached copy of PCT/IB/308)
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Item 11. to 16. below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A **FIRST** preliminary amendment.
    [ ] A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT/IPEA/409), INTERNATIONAL SEARCH REPORT (PCT/ISA/210), APPLICATION DATA SHEET, ABSTRACT

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NO.
10/009532	PCT/EP00/05356	9623 V/vmf/as

CALCULATIONS PTO USE ONLY

17. [X] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):

Neither international preliminary examination fee (37 CFR1.482) nor international search fee (37 CFR1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... $ 1,040.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... $ 890.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... $ 740.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... $ 710.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... $ 100.00

			ENTER APPROPRIATE BASIC FEE AMOUNT =	$	890.00
Surcharge of $130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492(e)).				$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$	
Total claims	14 - 20 =	0	X $18.00	$	
Independent claims	1 - 3 =	0	X $84.00	$	
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)			+ $280.00	$	
			TOTAL OF ABOVE CALCULATIONS =	$	890.00
Reduction of ½ for filing by small entity, if applicable. Applicant claims Small Entity Status under 37 CFR 1.27			+	$	445.00
			SUBTOTAL =	$	445.00
Processing fee of $130 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR1.492(f)).				$	
			TOTAL NATIONAL FEE =	$	445.00
Fee for recording the enclosed assignment (37 CFR1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property			+	$	40.00
			TOTAL FEES ENCLOSED =	$	485.00
				Amount to be refunded:	
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a. [X] A check in the amount of $ **485.00** to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. **25-0120** in the amount of $ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required by 37 CFR 1.16 and 1.17, or credit any overpayment to Deposit Account No. **25-0120**. A duplicate copy of this sheet is enclosed.

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December 12, 2001

By Benoit Castel
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PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Roberto VILLA et al.

Serial No. (unknown)

Filed herewith

CONTROLLED RELEASE AND TASTE MASKING
ORAL PHARMACEUTICAL COMPOSITIONS

PRELIMINARY AMENDMENT

Commissioner for Patents

Washington, D.C. 20231

Sir:

Prior to the first Official Action and calculation of the filing fee, please substitute Claims 1-15 as originally filed, which appear on pages 19-21, with Claims 1-14 as filed in the Article 34 amendment of June 4, 2001. The pages containing Claims 1-14 are marked "AMENDED SHEET" and are attached hereto. Following the insertion of Claims 1-14, please amend these claims as follows:

IN THE CLAIMS:

Please amend claims 3-5, 7, 9-11 and 13-14 as follows:

--3.(Amended) Composition as claimed in claim 1 in which the amphiphilic compounds are polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolamine), ceramides, glycol alkyl ethers, esters of fatty acids with polyethylene glycols or diethylene glycols.

4. (Amended) Compositions as claimed in claim 1, in which the lipophilic matrix consists of compound selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, mono-, di- or triglycerids of fatty acids, the polyethoxylated derivatives thereof, waxes, cholesterol derivatives.

5. (Amended) Compositions as claimed in claim 1, in which the hydrophilic matrix consists of hydrogel-forming compounds.

7. (Amended) Compositions as claimed in claim 1, comprising a gastro-resistant coating.

9. (Amended) Compositions as claimed in claim 1, in which the active ingredient is wholly contained in the inert /amphiphilic matrix, in the form of tablets, capsules or minitablets.

10. (Amended) Compositions as claimed in claim 1 in which the active ingredient is dispersed both in the hydrophylic matrix and in the lipophilic/amphiphilic matrix, in the form of tablets, capsules or minitablets.

11. (Amended) Compositions as claimed in claim 1, in which the active ingredient belongs to the therapeutical classes of analgesics, antitussives, bronchodilators,

antipsychotics, selective ß 2 antagonists, calcium antagonists, antiparkinson drugs, non-steroidal antiinflammatory drugs, antihistamines, antidiarrheals and intestinal antiinflammatories, apasmolytics, anxiolytics, oral antidiabetics, cathartics, antiepileptics, topical antimicrobials.

13.(Amended) Compositions as claimed in claim 1, containing bioadhesive substances.

14.(Amended) Pharmaceutical compositions as claimed in claim 1, in the form of tablets chewable or erodible in the buccal cavity or in the first portion of the gastrointestinal tract.--

IN THE ABSTRACT:

Please delete the abstract as originally filed which appears on the cover page of the Published Application. Add new abstract as enclosed herewith on a separate sheet.

REMARKS

The above changes in the claims merely place this national phase application in the same condition as it was during Chapter II of the international phase, with the multiple dependencies being removed. Following entry of this amendment by substitution of the pages, only claims 1-14 remain pending in this application. Claims 3-5, 7, 9-11 and 13-14 were amended to correct multiple dependency. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE"**.

Respectfully submitted,

YOUNG & THOMPSON

By _____

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December 12, 2001

"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

Claims 3-5, 7, 9-11 and 13-14 have been amended as follows:

3. (Amended) Composition as claimed in ~~any one of claims 1 to 2~~claim 1 in which the amphiphilic compounds are polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolamine), ceramides, glycol alkyl ethers, esters of fatty acids with polyethylene glycols or diethylene glycols.

4. (Amended) Compositions as claimed in claim 1, ~~2 or 3,~~ in which the lipophilic matrix consists of compound selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, mono-, di- or triglycerids of fatty acids, the polyethoxylated derivatives thereof, waxes, cholesterol derivatives.

5. (Amended) Compositions as claimed in ~~any one of the above claims,~~claim 1, in which the hydrophilic matrix consists of hydrogel-forming compounds.

7. (Amended) Compositions as claimed in ~~any one of the above claims,~~claim 1, comprising a gastro-resistant coating.

9. (Amended) Compositions as claimed in ~~any one of the above claims,~~claim 1, in which the active ingredient is wholly contained in the inert /amphiphilic matrix, in the form of tablets, capsules or minitablets.

10. (Amended) Compositions as claimed in ~~any one of claims 1 to 9~~claim 1 in which the active ingredient is dispersed both in the hydrophylic matrix and in the lipophilic/amphiphilic matrix, in the form of tablets, capsules or minitablets.

11. (Amended) Compositions as claimed in ~~any one of the above claims,~~claim 1, in which the active ingredient belongs to the therapeutical classes of analgesics, antitussives, bronchodilators, antipsychotics, selective ß 2 antagonists, calcium antagonists, antiparkinson drugs, non-steroidal antiinflammatory drugs, antihistamines, antidiarrheals and intestinal antiinflammatories, apasmolytics, anxiolytics, oral antidiabetics, cathartics, antiepileptics, topical antimicrobials.

13. (Amended) Compositions as claimed in ~~any one of the above claims,~~claim 1 containing bioadhesive substances.

14. (Amended) Pharmaceutical compositions as claimed in ~~the above claims~~, in the form of tablets chewable or erodible in the buccal cavity or in the first portion of the gastrointestinal tract.

CLAIMS

1. Controlled release and taste-masking oral pharmaceutical compositions containing an active ingredient, comprising:

a) a matrix consisting of C_6-C_{20} alcohols or C_8-C_{20} fatty acids or esters of fatty acids with glycerol or sorbitol or other polyalcohols with carbon atom chain not higher than six;

b) an amphiphilic matrix;

c) an outer hydrophilic matrix in which the lipophilic matrix and the optional amphiphilic matrix are dispersed;

d) optionally other excipients.

2. Controlled release compositions as claimed in claim 1 comprising a lipophilic or inert matrix consisting of lipophilic compounds with melting point below 90°C in which the active ingredient is at least partially inglobated and a hydrophilic matrix.

3. Compositions as claimed in any one of claims 1 to 2 in which the amphiphilic compounds are polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolamine), ceramides, glycol alkyl ethers, esters of fatty acids with polyethylene glycols or diethylene glycols.

4. Compositions as claimed in claim 1, 2 or 3, in which the lipophilic matrix consists of compound selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, mono-, di- or triglycerids of fatty acids, the polyethoxylated derivatives thereof, waxes, cholesterol derivatives.

5. Compositions as claimed in any one of the above claims, in which the hydrophilic matrix consists of

hydrogel-forming compounds.

6. Compositions as claimed in claim 5 in which the hydrophilic matrix consists of compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkylcellulose, carboxyalkylcellulose, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, natural or synthetic gums, polyalcohols.

7. Compositions as claimed in any one of the above claims, comprising a gastro-resistant coating.

8. Compositions as claimed in claim 7, in which the gastro-resistant coating consists of methacrylic acid polymers or cellulose derivatives.

9. Compositions as claimed in any one of the above claims, in which the active ingredient is wholly contained in the inert/amphiphilic matrix, in the form of tablets, capsules or minitablets.

10. Compositions as claimed in any one of claims 1 to 9 in which the active ingredient is dispersed both in the hydrophilic matrix and in the lipophilic/amphiphilic matrix, in the form of tablets, capsules or minitablets.

11. Compositions as claimed in any one of the above claims, in which the active ingredient belongs to the therapeutical classes of analgesics, antitussives, bronchodilators, antipsychotics, selective β 2 antagonists, calcium antagonists, antiparkinson drugs, non-steroidal antiinflammatory drugs, antihistamines, antidiarrheals and intestinal antiinflammatories, spasmolytics, anxiolytics, oral antidiabetics, cathartics, antiepileptics, topical antimicrobials.

12. Compositions as claimed in claim 10, in which the active ingredient is selected from mesalazine (5-aminosalicylic acid), budesonide, metformin, octylonium

bromide, gabapentin, carbidopa, nimesulide, propionylilcarnitine, isosorbide mono- and dinitrate, naproxen, ibuprofen, ketoprofen, diclofenac, thiaprophenic acid, nimesulide, chlorhexidine, benzydamine, tibezonium iodide, cetylpyridinium chloride, benzalkonium chloride, sodium fluoride.

13. Compositions as claimed in any one of the above claims, containing bioadhesive substances.

14. Pharmaceutical compositions as claimed in the above claims, in the form of tablets chewable or erodible in the buccal cavity or in the first portion of the gastrointestinal tract.

CONTROLLED RELEASE AND TASTE MASKING ORAL PHARMACEUTICAL COMPOSITIONS

The present invention relates to controlled release and taste-masking compositions containing one or more active principles incorporated in a three-component matrix structure, i.e. a structure formed by successive amphiphilic, lipophilic or inert matrices and finally incorporated or dispersed in hydrophilic matrices. The use of a plurality of systems for the control of the dissolution of the active ingredient modulates the dissolution rate of the active ingredient in aqueous and/or biological fluids, thereby controlling the release kinetics in the gastrointestinal tract, and it also allows the oral administration of active principles having unfavourable taste characteristics or irritating action on the mucosae of the administration site, particularly in the buccal area.

The compositions of the invention can contain active principles belonging to the therapeutical classes of analgesics, antiinflammatories, cardioactives, tranquillizers, antihypertensives, disinfectants and topical antimicrobials, antiparkinson drugs, antihistamines and are suitable to the oral administration or for acting topically at some areas of the gastrointestinal tract.

TECHNOLOGICAL BACKGROUND

The preparation of a sustained, controlled, delayed or anyhow modified release form can be carried out according to different known techniques:

1. The use of inert matrices, in which the main component of the matrix structure opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids; such property being known as lipophilia.

2. The use of hydrophilic matrices, in which the main component of the matrix structure opposes high resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases viscosity inside the hydrated layer.

3. The use of bioerodible matrices, which are capable of being degraded by the enzymes of some biological compartment.

All the procedures listed above suffer, however, from drawbacks and imperfections.

Inert matrices, for example, generally entail non-linear, but esponential, release of the active ingredient.

Hydrophilic matrices have a linear behaviour until a certain fraction of active ingredient has been released, then they significantly deviate from linear release.

Bioerodible matrices are ideal to carry out the so-called "site-release", but they involve the problem of finding the suitable enzyme or reactive to degradation. Furthermore, they frequently release in situ metabolites that are not wholly toxicologically inert.

A number of formulations based on inert lipophilic matrices have been described: Drug Dev. Ind. Pharm. 13 (6), 1001-1022, (1987) discloses a process making use of varying amounts of colloidal silica as a porization element for a lipophilic inert matrix in which the active ingredient is incorporated.

The same notion of canalization of an inert matrix is described in US 4,608,248 in which a small amount of a hydrophilic polymer is mixed with the substances forming an inert matrix, in a non sequential compenetration of different matrix materials.

EP 375,063 discloses a technique for the preparation of multiparticulate granules for the controlled-release of

the active ingredient which comprises co-dissolution of polymers or suitable substances to form a inert matrix with the active ingredient and the subsequent deposition of said solution on an inert carrier which acts as the core of the device. Alternatively, the inert carrier is kneaded with the solution containing the inert polymer and the active ingredient, then the organic solvent used for the their dissolution is evaporated off to obtain a solid residue. The resulting structure is a "reservoir", i.e. is not macroscopically homogeneous along all the symmetry axis of the final form.

The same "reservoir" structure is also described in Chem. Pharm. Bull. 46 (3), 531-533,, (1998) which improves the application through an annealing technique of the inert polymer layer which is deposited on the surface of the pellets.

To the "reservoir" structure also belong the products obtained according to the technique described in WO 93/00889 which discloses a process for the preparation of pellets in hydrophilic matrix which comprises:

- dissolution of the active ingredient with gastro-resistant hydrophilic polymers in organic solvents;
- drying of said suspension;
- subsequent kneading and formulation of the pellets in a hydrophilic or lipophilic matrix without distinction of effectiveness between the two types of application.

EP 0 453 001 discloses a multiparticulate with "reservoir" structure inserted in a hydrophilic matrix. The basic multiparticulate utilizes two coating membranes to decrease the release rate of the active ingredient, a pH-dependent membrane with the purpose of gastric protection and a pH-independent methacrylic membrane with the purpose of slowing down the penetration of the aqueous fluid.

WO 95/16451 discloses a composition only formed by a

hydrophilic matrix coated with a gastro-resistant film for controlling the dissolution rate of the active ingredient.

When preparing sustained-, controlled- release dosage forms of a medicament topically active in the gastrointestinal tract, it is important to ensure a controlled release from the first phases following administration, i.e. when the inert matrices have the maximum release rate inside the logarithmic phase, namely the higher deviation from linear release.

Said object has been attained according to the present invention, through the combination of an amphiphilic matrix inside an inert matrix, the latter formulated with a lipophilic polymer in a superficial hydrophilic matrix. The compositions of the invention are characterized by the absence of a first phase in which the medicament superficially present on the matrix is quickly solubilized, and by the fact the the amphiphilic layer compensate the lack of affinity of the aqueous solvent with the lipophilic compounds forming the inner inert matrix.

DISCLOSURE OF THE INVENTION

The invention provides controlled release and taste masking oral pharmaceutical compositions containing an active ingredient, comprising:

a) a matrix consisting of lipophilic compounds with melting point lower than 90°C and optionally by amphiphilic compounds in which the active ingredient is at least partially incorporated;

b) optionally an amphiphilic matrix;

c) an outer hydrophilic matrix in which the lipophilic matrix and the optional amphiphilic matrix are dispersed;

d) optionally other excipients.

A particular aspect of the invention consists of controlled release oral compositions containing one or more

active ingredients comprising:

a) a matrix consisting of amphiphilic compounds and lipophilic compounds with melting point below 90°C in which the active ingredient is at least partially incorporated;

b) an outer hydrophilic matrix in which the lipophilic/amphiphilic matrix is dispersed;

c) optional other excipients.

A further aspect of the invention provides taste masking oral pharmaceutical compositions containing one or more active ingredients comprising:

- an inert or lipophilic matrix consisting of C6-C20 alcohols or C8-C20 fatty acids or esters of fatty acids with glycerol or sorbitol or other polyalcohols with carbon atom chain not higher than six;

- an amphiphilic matrix consisting of polar lipids of type I or II or glycols partially etherified with C1-C4 alkyl chains;

- an outer hydrophilic matrix containing the above matrices, mainly formed by saccharide, dextrin, polyalcohol or cellulose compounds or by hydrogels;

- optional excipients to give stability to the pharmaceutical formulation.

DETAILED DISCLOSURE OF THE INVENTION

The compositions of the invention can be prepared by a method comprising the following steps:

a) the active ingredient is first inglobated by simple kneading or mixing in a matrix or coating consisting of compounds having amphiphilic properties, which will be further specified below. The active principle(s) can be mixed with the amphiphilic compounds without the aid of solvents or with small amounts of water-alcoholic solvents.

b) The matrix obtained in a) is incorporated in a low melting lipophilic excipient or mixture of excipients, while heating to soften and/or melt the excipient itself,

which thereby incorporates the active ingredient by simple dispersion. After cooling at room temperature an inert matrix forms, which can be reduced in size to obtain inert matrix granules containing the active ingredient particles.

c) The inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellable excipients. The mixture is then subjected to compression or tabletting. This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" caused by the dissolution of the medicament inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix.

The amphiphilic compounds which can be used according to the invention comprise polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolamine), ceramides, glycol alkyl ethers such as diethylene glycol monomethyl ether (Transcutol$^{(R)}$).

The lipophilic matrix consists of substances selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerids, the polyethoxylated derivatives thereof, waxes, ceramides, cholesterol derivatives or mixtures thereof having melting point within the range of 40 to 90°C, preferably from 60 to 70°C.

If desired, a fatty acid calcium salt may be incorporated in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside.

According to an embodiment of the invention, an amphiphilic matrix with high content in active ingredient, typically from 5 to 95% w/w, is first prepared by dispersing the active ingredient or the mixture of active ingredients in a mixture of amphiphilic compounds, such as lecithin, other type II polar lipids, surfactants, or in diethylene glycol monoethyl ether; the resulting amphiphilic matrix is then mixed or kneaded, usually while hot, with lipophilic compounds suitable to form an inert matrix, such as saturated or unsaturated fatty acids, such as palmitic, stearic, myristic, lauric, laurylic, or oleic acids or mixtures thereof with other fatty acids with shorter chain, or salts or alcohols or derivatives of the cited fatty acids, such as mono-, di-, or triglycerids or esters with polyethylene glycols, alone or in combination with waxes, ceramides, cholesterol derivatives or other apolar lipids in various ratios so that the melting or softening points of the lipophilic compounds mixtures is within the range of 40° to 90°C, preferably from 60 to 70°C.

Alternatively, the order of formation of the inert and amphiphilic matrices can be reversed, incorporating the inert matrix inside the amphiphilic compounds.

The resulting inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture.

The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which when passing from the dry state to the hydrated one, undergo the so-called "molecular relaxation", namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves.

Examples of hydrogels which can be used according to the invention are compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid.

In case of taste-masking formulations, the use of polyalcohols such as xylitol, maltitol and mannitol as hydrophilic compounds can also be advantageous.

The lipophilic matrix granules containing the active ingredient are mixed with the hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:50 (lipophilic matrix: hydrophilic matrix). Part of the active ingredient can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the hydrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or minitablets.

The compression of the mixture of lipophilic and/or amphiphilic matrix, hydrogel-forming compound and, optionally, active ingredient not inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix. A similar result can also be obtained by coating the lipophilic matrix granules with a hydrophilic polymer coating.

The tablets obtainable according to the invention can optionally be subjected to known coating processes with a gastro-resistant film, consisting of, for example, methacrylic acids polymers (Eudragit(R)) or cellulose derivatives, such as cellulose acetophthalate.

Active ingredients which can conveniently be formulated according to the invention comprise:

- analgesics, such as acetaminophen, phenacetin, sodium salicylate;
- antitussives, such as dextromethorphan, codeine phosphate;
- bronchodilators, such as albuterol, procaterol;
- antipsychotics, such as haloperidol, chlorpromazine;
- antihypertensives and coronary-dilators, such as isosorbide mono- and dinitrate, captopril;
- selective ß 2 antagonists such as salbutamol, terbutaline, ephedrine, orciprenaline sulfate;
- calcium antagonists, such as nifedipine, nicardipine, diltiazem, verapamil;
- antiparkinson drugs, such as pergolide, carpidopa, levodopa;
- non steroid anti-inflammatory drugs, such as ketoprofen, ibuprofen, diclofenac, diflunisal, piroxicam, naproxen, ketorolac, nimesulide, thiaprophenic acid, mesalazine (5-aminosalicylic acid);
- antihistamines, such as terfenedine, loratadine;
- antidiarrheals and intestinal antiinflammatories, such as loperamide, 5-aminosalicylic, olsalazine, sulfasalazine, budenoside;
- spasmolytics such as octylonium bromide;
- anxiolytics, such as chlordiazepoxide, oxazepam, medazepam, alprazolam, donazepam, lorazepan;
- oral antidiabetics, such as glipizide, metformin, phenformin, gilclazide, glibenclamide;
- cathartics, such as bisacodil, sodium picosulfate;
- antiepileptics, such as valproate, carbamazepine, phenytoin, gabapentin;
- antitumorals, such as flutamide, etoposide;
- oral cavity disinfectants or antimicrobials, such

as benzalkonium chloride, cetylpyridinium chloride or tibezonium iodide, and some amino derivatives such as benzydamine and chlorhexidine as well as the salts and derivatives thereof;

- sodium fluoride.

The compositions of the invention can further contain conventional excipients, for example bioadhesive excipients such as chitosans, polyacrylamides, natural or synthetic gums, acrylic acid polymers.

The compositions of the invention can contain more than one active ingredient, each of them being optionally contained in the hydrophilic matrix or in the inert amphiphilic matrix, and are preferably in the form of tablets, capsules or minitablets.

In terms of dissolution characteristics, contact with water or aqueous fluids causes the immediate penetration of water inside the more superficial layer of the matrix which, thanks to the presence of the aqueous solvent, swells due to the distension of the polymeric chains of the hydrogels, giving rise to a high viscosity hydrated front which prevents the further penetration of the solvent itself linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness, until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of inert matrix granules, however induces the diffusion mechanism typical of these structures and therefore further slows down the dissolution profile of the active ingredient.

The presence of the amphiphilic matrix inside the lipophilic matrix inert allows to prevent any unevenness of the release profile of the active ingredient. The surfactants present in the amphiphilic portion promote

wettability of the porous canaliculuses which cross the inert matrix preventing or reducing resistance to penetration of the solvent inside the inert matrix.

To obtain taste masking tablets, the components of the hydrophilic matrix are carefully selected to minimize the active substance release time through penetration accelerated by the canalization induced by the hydrophilic compound.

The following Examples illustrate the invention in greater detail.

EXAMPLE 1

500 g of 5-aminosalicylic acid and 20 g of octylonium bromide are mixed with 10 g of soy lecithin dissolved in 50 g of a water : ethyl alcohol 1:3 mixture at about 50°C. After homogenization and drying, the granules of the resulting matrix are treated in a kneader with 20 g of carnauba wax and 50 g of stearic acid, heating until homogeneous dispersion, then cold-extruded into small granules. The inert matrix granules are loaded into a mixer in which 30 g of carbopol 971 P and 65 g of hydroxypropyl methylcellulose are sequentially added. After a first mixing step for homogeneously dispersing the powders, 60 g of microcrystalline cellulose and 5 g of magnesium stearate are added. After mixing, the final mixture is tabletted to unitary weight of 760 mg/tablet. The resulting tablets are film-coated with cellulose acetophthalate or polymethacrylates and a plasticizer to provide gastric resistance and prevent the early release of product in the stomach.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 30%, after 180 minutes no more than 60%, after 5 hours no more than 80%.

EXAMPLE 2

50 g of diethylene glycol monoethyl ether are homogeneously distributed on 500 g of microcrystalline cellulose; then 100 g of Budesonide are added, mixing to complete homogenization. This mix is further added with 400 g of Budesonide, then dispersed in a blender containing 100 g of carnauba wax and 100 g of stearic acid preheated at a temperature of 60°C. After kneading for 5 minutes, the mixture is cooled to room temperature and extruded in granules of size below 1 mm.

A suitable mixer is loaded with the matrix granules prepared as above and the following amounts of hydrophilic excipients: 1500 g of hydroxypropyl methylcellulose and 500 g of policarbophil.

The components are mixed until homogeneous dispersion of the matrices, then added with 2450 g of microcrystalline cellulose, 400 g of lactose, 100 g of colloidal silica and 50 g of magnesium stearate. After further 5 minute mixing, the mix is tabletted to unitary weight of 250 mg/tablet.

EXAMPLE 3

850 g of metformin are dispersed in a granulator/kneader with 35 g of diethylene glycol monoethyl ether previously melted with 100 g of stearic acid and 55 g of carnauba wax. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 1040 g of formulation are added with 110 g of hydroxypropyl methylcellulose and 20 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 1170 mg/tablet equivalent to 850 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 35%, after 180 minutes no more than

60%, after 5 hours no more than 80%.

EXAMPLE 4

120 g of octylonium bromide are dispersed in a granulator/kneader with 30 g of stearic acid and 15 g of beeswax in which 10 g of diethylene glycol monoethylene had previously been melted.

The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 10 g of formulation are added with 5 g of hydroxypropyl methylcellulose and 5 g of policarbophyl, 2 g of magnesium stearate and 3 g of microcrystalline cellulose.

The final mixture is tabletted to unitary weight of 200 mg/tablet equivalent to 120 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 25%; after 180 minutes no more than 50%; after 5 hours no more than 70%.

EXAMPLE 5

12 g of diethylene glycol monoethyl ether are loaded on 6 g of microcrystalline cellulose and 6 grams of calcium carbonate, then 100 g of Gabapentin are added and the mixture is homogenized. After that, 800 g of Gabapentin are added which are dispersed in a granulator/kneader with 4.5 g of white wax and 5 g of stearic acid. The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 916.5 g of formulation are added with 39.5 g of hydroxypropyl methylcellulose, 10 g of alginic acid, 11 g of magnesium stearate and 6 g of syloid. The final mixture is tabletted to unitary weight of 1000 mg/tablet equivalent to 900 mg of active ingredient.

EXAMPLE 6

50 g (25 g) of carbidopa and 200 g (100 g) of levodopa

are dispersed in a granulator/kneader with 60 g (30 g) of stearic acid and 30 g (15 g) of yellow wax, in which 10 (5) g of diethylene glycol monoethyl ether had previously been melted.

The system is heated to carry out the granulation of the active ingredient in the inert matrix. The resulting 340 g (170 g) of formulation are added with 20 g (10 g) of hydroxypropyl methylcellulose, 10 g (5 g) of xantangum, 16 g (8 g) of microcrystalline cellulose, 4 g (2 g) of magnesium stearate.

The final mixture is tabletted to unitary weight of 400 (200) mg/tablet equivalent to 50(25) mg of carbidopa and 200 (100) mg di levodopa.

EXAMPLE 7

4 g of Nimesulide are solubilised in 50 g of diethylene glycol monoethyl ether, then 100 g of microcrystalline cellulose are added to obtain a homogeneous mixture.

The resulting mixture is added in a granulator/kneader with 196 g of Nimesulide, 50 g of stearic acid and 25 g of carnauba wax. The system is heated to carry out the granulation of the active ingredient in the inert and amphiphilic matrix system.

425 g of the resulting granulate are added with 60 g of hydroxypropyl methylcellulose, 5 g of policarbophil and 10 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 500 mg/tablet equivalent to 200 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 1 hour no more than 25%, after 2 hours no more than 40%, after 4 hours no more than 60%, after 8 hours no more than 90%.

EXAMPLE 8

500 g of propionyl carnitine are dispersed in a granulator/kneader with 90 g of stearic acid and 40 g of carnauba wax, in which 20 g of diethylene glycol monoethyl ether had previously been melted. The system is heated to carry out the granulation of the active ingredient in the inert/amphiphilic matrix. The resulting 650 g of formulation are added with 60 g of hydroxypropyl methylcellulose and 10 g of magnesium stearate.

The final mixture is tabletted to unitary weight of 720 mg/tablet equivalent to 500 mg of active ingredient.

The resulting tablets, when subjected to dissolution test in simulated enteric juice, have shown a release of the active principles having the following profile: after 60 minutes no more than 40%, after 180 minutes no more than 60%, after 4 hours no more than 80%, after 8 hours no more than 90%.

EXAMPLE 9

One kg of Nimesulide is placed in a high rate granulator, pre-heated to about 70°, together with 200 g of cetyl alcohol and 25 g of glycerol palmitostearate; the mixture is kneaded for about 15 minutes and stirred while decreasing temperature to about 30°C. The resulting inert matrix is added, keeping stirring and kneading during cooling, with 50 g of soy lecithin and 50 g of ethylene glycol monoethyl ether. The granulate is extruded through a metallic screen of suitable size and mixed with 50 g of hydroxypropyl methylcellulose, 1320 kg of maltodextrins, 2 kg of lactose-cellulose mixture, 50 g of colloidal silica, 40 g of aspartame, 150 g of citric acid, 75 g of flavour and 65 g of magnesium stearate. The final mixture is tabletted to unitary weight of about 500 mg, having hardness suitable for being dissolved in the mouth and a pleasant taste.

EXAMPLE 10

Operating as in the preceding example, chewable tablets are prepared replacing dextrin with mannitol and the lactose-cellulose mixture with xylitol. The resulting tablets ahve pleasant taste and give upon chewing a sensation of freshness enhancing the flavour.

EXAMPLE 11

Operating as described in example 9, but with the following components:

-	active ingredient: ibuprofen	mg 100
-	lipophilic/inert matrix component:	
	cetyl alcohol	mg 15
-	amphiphilic matrix component:	
	soy lecithin	mg 8
-	hydrophilic matrix components: mannitol	mg 167
-	maltodextrins	mg 150
-	methylhydroxypropylcellulose	mg 30
-	adjuvants: aspartame	mg 15
-	flavour	mg 5
-	colloidal silica	mg 5
-	magnesium stearate	mg 5

500 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the bitter, irritating taste of the active ingredient.

EXAMPLE 12

Operating as described in example 9, but with the following components:

-	active ingredient: diclofenac sodium	mg 25
-	lipophilic/inert matrix component:	
	cetyl alcohol	mg 5
-	glycerol palmitostearate	mg 5
-	amphiphilic matrix component:	
	soy lecithin	mg 7

- hydrophilic matrix components: xylitol mg 168
- maltodextrins mg 150
- hydroxypropylmethylcellulose mg 20
- adjuvants: aspartame mg 5
- flavour mg 5
- colloidal silica mg 5
- magnesium stearate mg 5

400 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the irritating taste of the active ingredient.

EXAMPLE 13

Operating as described in example 9, but with the following components:

- active ingredient: chlorhexidine mg 2,5
- lipophilic/inert matrix component:
  cetyl alcohol mg 0.5
- glycerol palmitostearate mg 0.5
- amphiphilic matrix component:
  diethylene glycol monoethyl ether mg 0.3
- hydrophilic matrix components: xylitol mg 38
- maltodextrins mg 96
- hydroxypropyl methylcellulose mg 10
- adjuvants: aspartame mg 3
- flavour mg 5
- colloidal silica mg 2
- magnesium stearate mg 2

150 mg unitary weight tablets are obtained, which undergo progressive erosion upon buccal administration, and effectively mask the irritating taste of the active ingredient.

EXAMPLE 14

One Kg of Nimesulide is placed in a high rate granulator, pre-heated to about 70°, together with g 125 of

cetyl alcohol: the mixture is kneaded for about 15 minutes and stirred while decreasing temperature to about 30°C, then added with g 30 of lecithin. The resulting matrix is then extruded through a metallic screen of suitable size and mixed with 2.415 kg of lactose, 1.0 kg of maltodextrins, 50 g of hydroxypropyl methylcellulose, 50 g of colloidal silica, 40 g of aspartame, 150 g of citric acid, 75 g of flavour and 65 g of magnesium stearate. The final mixture is tabletted to about 500 mg tablets, having hardness suitable for being dissolved in the mouth and pleasant taste.

CLAIMS

1. Controlled release and taste-masking oral pharmaceutical compositions containing an active ingredient, comprising:

a) a matrix consisting of C_6-C_{20} alcohols or C_8-C_{20} fatty acids or esters of fatty acids with glycerol or sorbitol or other polyalcohols with carbon atom chain not higher than six;

b) an amphiphilic matrix;

c) an outer hydrophilic matrix in which the lipophilic matrix and the optional amphiphilic matrix are dispersed;

d) optionally other excipients.

2. Controlled release compositions as claimed in claim 1 comprising a lipophilic or inert matrix consisting of lipophilic compounds with melting point below 90°C in which the active ingredient is at least partially inglobated and a hydrophilic matrix.

3. Compositions as claimed in any one of claims 1 to 2 in which the amphiphilic compounds are polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidyl-ethanolamine), ceramides, glycol alkyl ethers, esters of fatty acids with polyethylene glycols or diethylene glycols.

4. Compositions as claimed in claim 1, 2 or 3, in which the lipophilic matrix consists of compound selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, mono-, di- or triglycerids of fatty acids, the polyethoxylated derivatives thereof, waxes, cholesterol derivatives.

5. Compositions as claimed in any one of the above claims, in which the hydrophilic matrix consists of

hydrogel-forming compounds.

6. Compositions as claimed in claim 5 in which the hydrophilic matrix consists of compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkylcellulose, carboxyalkylcellulose, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, natural or synthetic gums, polyalcohols.

7. Compositions as claimed in any one of the above claims, comprising a gastro-resistant coating.

8. Compositions as claimed in claim 7, in which the gastro-resistant coating consists of methacrylic acid polymers or cellulose derivatives.

9. Compositions as claimed in any one of the above claims, in which the active ingredient is wholly contained in the inert/amphiphilic matrix, in the form of tablets, capsules or minitablets.

10. Compositions as claimed in any one of claims 1 to 9 in which the active ingredient is dispersed both in the hydrophilic matrix and in the lipophilic/amphiphilic matrix, in the form of tablets, capsules or minitablets.

11. Compositions as claimed in any one of the above claims, in which the active ingredient belongs to the therapeutical classes of analgesics, antitussives, bronchodilators, antipsychotics, selective β 2 antagonists, calcium antagonists, antiparkinson drugs, non-steroidal antiinflammatory drugs, antihistamines, antidiarrheals and intestinal antiinflammatories, spasmolytics, anxiolytics, oral antidiabetics, cathartics, antiepileptics, topical antimicrobials.

12. Compositions as claimed in claim 10, in which the active ingredient is selected from mesalazine (5-aminosalicylic acid), budesonide, metformin, octylonium

bromide, gabapentin, carbidopa, nimesulide, propionylilcarnitine, isosorbide mono- and dinitrate, naproxen, ibuprofen, ketoprofen, diclofenac, thiaprophenic acid, nimesulide, chlorhexidine, benzydamine, tibezonium iodide, cetylpyridinium chloride, benzalkonium chloride, sodium fluoride.

13. Compositions as claimed in any one of the above claims, containing bioadhesive substances.

14. Pharmaceutical compositions as claimed in the above claims, in the form of tablets chewable or erodible in the buccal cavity or in the first portion of the gastrointestinal tract.

9263V

Ref. _____

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Controlled release and taste masking oral pharmaceutical compositions

the specification of which: *(check one)*

REGULAR OR DESIGN APPLICATION

[ ] is attached hereto.

[ ] was filed on _____ as application Serial No. _____ and was amended on _____ (if applicable).

PCT FILED APPLICATION ENTERING NATIONAL STAGE

[x] was described and claimed in International application No. PCT/EP00/05356 filed on 09.06.2000 and as amended on _____ (if any).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

PRIORITY CLAIM

I hereby claim foreign priority benefits under 35 USC 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN APPLICATION(S)

Country	Application Number	Date of Filing (day, month, year)	Priority Claimed
Italy	MI99A001317	14.06.1999	YES
Italy	MI2000A000422	03.03.2000	YES

(Complete this part only if this is a continuing application.)

I hereby claim the benefit under 35 USC 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of 35 USC 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.) (Filing Date) (Status--patented, pending, abandoned)

Full name of fourth joint inventor, if any Lorenzo FOSSATI

Inventor's signature _____ 30.11.2001
Date

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Full name of fifth joint inventor, if any _____

Inventor's signature _____ Date

Residence _____

Citizenship _____

Post Office Address _____

Full name of sixth joint inventor, if any _____

Inventor's signature _____ Date

Residence _____

Citizenship _____

Post Office Address _____

Full name of seventh joint inventor, if any _____

Inventor's signature _____ Date

Residence _____

Citizenship _____

Post Office Address _____

Full name of eighth joint inventor, if any _____

Inventor's signature _____ Date

Residence _____

Citizenship _____

Post Office Address _____

POWER OF ATTORNEY

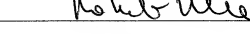
The undersigned hereby authorizes the U.S. attorney or agent named herein to accept and follow instructions from ___ _____ as to any action to be taken in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorney or agent and the undersigned. In the event of a change in the persons from whom instructions may be taken, the U.S. attorney or agent named herein will be so notified by the undersigned.

As a named inventor, I hereby appoint the following attorney(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: **Robert J. PATCH, Reg. No. 17,355, Andrew J. PATCH, Reg. No. 32,925, Robert F. HARGEST, Reg. No. 25,590, Benoît CASTEL, Reg. No. 35,041, Eric JENSEN, Reg. No. 37,855, and Thomas W. PERKINS, Reg. No. 33,027**, c/o YOUNG & THOMPSON, Second Floor, 745 South 23rd Street, Arlington, Virginia 22202.

Address all telephone calls to Young & Thompson at 703/521-2297.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor: Roberto VILLA
(given name, family name)

Inventor's signature  Date 30.11.2001

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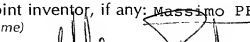
Full name of second joint inventor, if any: Massimo PEDRANI
(given name, family name)

Inventor's signature  Date 30.11.2001

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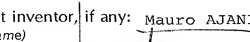
Inventor's signature  Date 30.11.2001

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